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Understanding emotion processing in schizophrenia

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Introduction

Schizophrenia

Schizophrenia is a complex psychiatric syndrome influenced by interactions between genetic and environmental risk factors. Schizophrenia is mostly regarded as a neurocognitive disorder (Heinrichs and Zakzanis, 1998) and most research has been directed at cognitive functioning. However, since its earliest descriptions emotional disturbances have been described as cardinal features of schizophrenia (Bleuler, 1911). Recently, it has been proposed that these emotional disturbances involving experience, expression and recognition of emotions might be at the core of the disease (Aleman and Kahn, 2005; Kohler et al., 2003). Studies identifying emotional deficits in schizophrenia are relatively scarce compared to studies examining cognitive processes, but in the last decades there is increasing interest in emotional processing in schizophrenia with the emphasis on emotion recognition (Chan et al., 2010; Hoekert et al., 2007). To get more insight in the underlying mechanisms of disturbances in affect, more research is needed into emotion regulation and its underlying processing. Moreover, the neural basis of emotion processing in schizophrenia should be further delineated. Furthermore, studies into the genetic basis related to emotion processing and schizophrenia are critical to get more insight into emotion processing in schizophrenia.

The goal of this thesis is to get a better understanding of emotion processing in schizophrenia. To achieve this we will first focus on healthy individuals with difficulties in emotion processing (i.e. alexithymia). Additionally, we will investigate emotion regulation and emotion processing difficulties in patients with schizophrenia and first-degree relatives of patients. Also, neural mechanisms underlying specific aspects of emotion processing will be examined in aforementioned groups. Further, the relationship between a genetic polymorphism, catechol-O-methyltransferase (COMT) Val158Met, brain activation during emotion processing and alexithymia will be explored.

Emotion processing

Emotions are important for social functioning. To build and maintain a social network interaction with other people is essential. Different emotional processes are crucial for this, such as recognizing the others emotions and identifying your own emotions. Emotion or emotion processing is a broad term and includes several aspects, e.g. emotion experience, emotion perception, emotional learning and emotion regulation. These processes are all interrelated and important for good personal and social functioning. Difficulties in emotion processing are a core feature of many psychiatric disorders such as depression, anxiety and presumably schizophrenia. To increase the understanding about how emotional disturbances affect functioning, illness course and outcome in psychiatric disorders, it is critical to identify which of these processes are disturbed and to disentangle them and their underlying neural correlates, both in healthy persons and in individuals with a psychiatric disorder.

Different neural systems have been suggested to be important for emotion processing. A ventral system, including amygdala, insula and ventral regions of the anterior cingulate cortex, is important for the identification of the emotional salience of a stimulus, the production of an affective state and the regulation of autonomic responses. A dorsal system, including dorsal regions of the anterior cingulate cortex and prefrontal cortex and hippocampus, is implicated in the effortful regulation of emotions (Phillips et

al., 2003a). Further, cortical midline structures, such as the posterior cingulate cortex and precuneus, have been associated with self-related processing and autobiographical memory (Maddock et al., 2003; Northoff et al., 2006; van der Meer et al., 2010). Changes in these structures have been associated with difficulties in emotion processing and may lead to symptoms related to psychiatric disorders (Phillips et al., 2003b).

Hence, the term emotion processing encompasses many facets. In this thesis we will focus on three different aspects: 1) emotion regulation, 2) associative emotional learning and 3) valence evaluation, which will be described later in this section.

Alexithymia and emotion processing

Alexithymia is a personality trait which has been related to difficulties in emotion processing. The word 'alexithymia' stems from the Greek *a* (lack), *lexis* (word) and *thymos* (emotion). It is a multidimensional construct consisting of difficulties in emotion regulation, difficulties in identifying, describing and communicating emotions, difficulties in differentiating feelings from bodily sensations and diminished affect-related fantasy (Nemiah and Sifneos, 1970; Sifneos, 1973). It is a dimensional personality trait that varies in degree from person to person. In a large sample in the general Finnish population, the prevalence rate of alexithymia was around 10% (Salminen et al., 1999). It has also been demonstrated in a large twin study that genetic factors have a noticeable influence on alexithymia (heritability around 30%) (Jorgensen et al., 2007).

Alexithymia has been related to reduced life satisfaction (Mattila et al., 2007). Importantly, alexithymia has been identified as a risk factor for a variety of medical and psychiatric disorders like substance use disorders, somatization, anxiety and depression (Taylor et al., 1997). Higher alexithymia scores in schizophrenia patients have been reported in previous studies (Cedro et al., 2001; van 't Wout et al., 2007; van der Meer et al., 2009). Unaffected relatives of schizophrenia patients with high alexithymia scores may have an increased vulnerability to develop schizophrenia (van 't Wout et al., 2007).

With regard to brain activation, some differences have been related to alexithymia (for a review see Aleman, 2005): anterior cingulate gyrus and insula, related to emotion regulation (Kano et al., 2003), posterior cingulate gyrus, associated with compromised retrieval of autobiographical memory (Mantani et al., 2005) and medial prefrontal cortex in relation to theory of mind (Moriguchi et al., 2006).

Schizophrenia and emotion processing

Schizophrenia is a severe and chronic psychiatric disease that affects approximately half to one percent of the population (McGrath et al., 2004). A study in the Netherlands on the course of schizophrenia demonstrated that 27 % of the patients showed complete remission, 11 % of the patients had a chronic psychosis and 43 % of the patients a negative syndrome (Wiersma et al., 1998).

Schizophrenia affects cognition, emotion and (social) behavior. Diagnostic criteria according to the DSM IV are delusions, hallucinations, disorganized speech and negative symptoms such as affective flattening, poverty of speech and lack of motivation (American Psychiatric Association, 1994). Schizophrenia typically develops in adolescence and early adulthood. Thus, it affects individuals at an often pivotal time in their personal, professional and social development.

Cognitive impairments are regarded as core features of schizophrenia and most emphasis has been placed on this aspect. Indeed, patients are most impaired on verbal memory, executive functioning and attention (e.g. Aleman et al., 1999; Heinrichs and Zakzanis, 1998). However, emotional deficits, described since the earliest descriptions (Bleuler, 1911), are also very important. Recently, it has been proposed that dysfunctioning of emotional brain systems might be as important as cognitive impairments for the understanding of schizophrenia (Aleman and Kahn, 2005; Kohler et al., 2003).

Emotion processing is an important aspect of social cognition (information processing underlying social interaction). Patients with schizophrenia who perform worse on social cognition tasks, have lower functional outcome such as independent living skills and social or professional functioning (for a meta-analysis see Fett et al. 2010). Importantly, performance on social cognition tasks predicts functional outcome and this association cannot be accounted for by cognitive deficits (Penn et al., 2000; Pinkham et al., 2003). Therefore, social cognition seems a very fruitful area of study.

As mentioned earlier, patients show abnormalities in emotion processing. There seems to be a disjunction between the expression, the experience and the psychophysiological components of emotion. Kring and Neale (1996) investigated these three domains within subjects and reported that during watching emotional films patients were less facially expressive than controls. In contrast, patients exhibited greater skin conductance reactivity during the films. Finally, after the films, they reported similar experience of positive and negative emotion. To explain these differences in emotional processing in schizophrenia, Aleman and Kahn (2005) hypothesized that deficits in emotion perception and expression are the result of volume reductions of the amygdala and decreased connectivity with the prefrontal cortex. An imbalance in dopamine might underlie the increased experience of emotion, associated with psychotic symptoms. However, more research into emotion processing and schizophrenia is needed to disentangle the underlying mechanisms of the emotional abnormalities.

With regard to neural correlates, schizophrenia has been associated with structural and functional abnormalities in brain regions associated with emotion processing. The amygdala, a key structure for emotion processing, has been shown to be differently activated in patients with schizophrenia during emotional processing (Aleman and Kahn, 2005). Also, other regions important for emotional processing have been demonstrated to show different activation patterns in schizophrenia patients, e.g. the dorsolateral prefrontal cortex, medial prefrontal cortex, cingulate gyrus and insula (Phillips et al., 2003b). Further, differences in connectivity between brain regions have been observed during tasks (Meyer-Lindenberg et al., 2005) and during the resting state (Calhoun et al., 2009).

As stated above, schizophrenia has been associated with imbalances in dopaminergic neurotransmission. Hyperactivity of the subcortical dopaminergic pathways is postulated to mediate psychotic symptoms while hypoactivity of prefrontal dopaminergic pathways may cause the negative and cognitive symptoms (van Os and Kapur, 2009). Vulnerability for schizophrenia is partly genetic as evidenced by the following observations. The incidence in the general population is around 0.5 - 1% but the chance of having it when a sibling has it is up to ten times higher. When a monozygotic twin has it, the incidence is around 50% (Gottesman, 1991). A gene which has been related to both dopamine transmission and brain activation in the prefrontal

cortex is the catechol-O-methyltransferase (COMT) gene. As schizophrenia has been associated with both dysregulation of the dopamine system and of the prefrontal cortex, the COMT gene has been related to schizophrenia and abnormalities in first-degree relatives (Tunbridge et al., 2006).

Relatives and emotion processing

The liability to schizophrenia is heritable, as shown through patterns of risk in twins and other family members. A major limitation of studying patients is the bias induced by the antidopaminergic effect of antipsychotic medication, which almost all patients use at some stage of their illness. This limitation could be circumvented by studying people with an increased risk to develop schizophrenia instead of patients. In addition, studying high-risk individuals without psychosis has no confounds of chronicity of the illness, antipsychotic medication use, severe cognitive deficits or hospitalisation. Studying high-risk groups adds insight into the pathophysiology of schizophrenia and may help to identify traits that are presumably core parts of the liability to the disorder.

Interestingly, non-affected relatives of schizophrenia patients have been shown to be impaired on a range of cognitive tasks, especially on memory performance and executive functioning although less severe than patients (Keshavan, 2010; Sitskoorn et al., 2004). Moreover, deficits in social function are present throughout the course of schizophrenia in a large proportion of the patient population (Wiersma et al., 2000) and have been reported in relatives of schizophrenia patients as well (Hans et al., 2000). Emotion processing is important for social cognition. Knowledge of emotion processing and its neural correlates in first-degree relatives is relatively scarce. Phillips and Seidman (2008) reported in their review that at-risk groups demonstrate similar abnormalities as schizophrenia patients but at an attenuated level. The most robust findings are in the areas of reduced emotion perception, self-reported anhedonia, and increased negative affect (Phillips and Seidman, 2008). In addition, van 't Wout (2007) investigated alexithymic traits in patients and first-degree relatives. Male siblings reported more difficulties in verbalizing their feelings than controls and appeared to fantasize less.

Only a few studies have been conducted into the neural correlates underlying emotion processing in relatives. Structural and functional brain alterations in relatives have been found in multiple brain areas that are relevant to emotion processing including the prefrontal cortex, amygdala, amygdala-hippocampal complex and the hippocampus (Phillips and Seidman, 2008).

Imaging Genetics

Psychiatric syndromes are often complex and generally not the result of one gene or a specific combination of genes. It has not been easy to find a genetic mechanism underlying schizophrenia. Imaging genetics is a strategy to investigate the effect of a genotype on brain function (in this case an endophenotype). An endophenotype or intermediate phenotype is a measurable component (e.g. working memory performance or brain activation during a task) that lies between the predisposing genes and the disease phenotype. The endophenotype found in affected family members, has to be present in non-affected relatives in a higher rate than in the general population. In addition, the endophenotype should be state independent. The endophenotype may represent more direct clues to the genetic underpinnings than the disease itself (cf.

Gottesman and Gould, 2003). Thus, gene effects explaining neural mechanisms underlying differences in emotional processing could help clarify emotional disturbances both in the healthy population and in schizophrenia.

Catechol-O-methyltransferase (COMT) gene and emotion processing

One of the genes that has received much interest in the field of emotion processing and psychiatric disorders is the catechol-O-methyltransferase (COMT) gene. The COMT gene codes for the COMT enzyme. This is a major enzyme involved in the inactivation of the catecholamine neurotransmitters including dopamine, epinephrine, and norepinephrine. Catecholaminergic neurotransmission is of prime importance in regulating neural circuits involved in cognitive and affective processing (Heinz and Smolka, 2006). The COMT gene has a functional variant involving the substitution of valine (Val) for methionine (Met) at codon 158 (Val158Met). The Met allele is associated with low enzymatic activity resulting in higher levels of prefrontal dopamine. Conversely, the Val allele is associated with high enzymatic activity and lower levels of prefrontal dopamine (Lachman et al., 1996; Mannisto and Kaakkola, 1999). Given the association between schizophrenia and decreased dopamine activity in the prefrontal cortex, schizophrenia has been linked to the COMT Val158Met polymorphism but with inconsistent results (Okochi, 2009).

The Met allele has been associated with better cognitive processing (Egan et al., 2001) but worse emotion processing (Weiss et al., 2007a). Studies of the neural correlates associated with the COMT Val158Met genotype have mainly focused on cognitive processing but also a few emotion processing studies have been done, again with inconsistent results. Both decreased and increased activation related to having more Met alleles has been reported in prefrontal areas during emotional tasks. In addition, less activation in amygdala and right temporal pole during labeling facial expressions has been shown in Met homozygotes whereas an increased activation has been shown in right hippocampal formation and right ventrolateral prefrontal cortex during matching facial expressions (for a review see Mier et al., 2010).

Given this relationship between emotional processing and COMT, relevant for dopamine transmission, we hypothesized that this polymorphism would be associated with difficulties in emotion processing and its underlying neural mechanisms.

Outline of the dissertation

In this dissertation, we present research that examines various aspects of emotion processing. We use behavioral measures, functional magnetic resonance imaging (fMRI) and imaging genetics. We examine emotion processing in healthy participants with high versus low levels of alexithymia. In addition, we investigate the neural basis of emotion regulation in patients with schizophrenia, non-psychotic first-degree relatives and the relationship with alexithymia. Further, we examine a specific aspect of emotion processing, i.e. associative emotional learning, more thoroughly in patients with schizophrenia. Finally, we study the effect of a genetic polymorphism, COMT Val158Met, on brain activation related to valence evaluation, as well as the association between COMT and alexithymia.

The *second chapter* describes behavioral correlates of different stages of emotion processing and emotion regulation strategies in individuals with alexithymia. Previous studies of alexithymia focused on one stage of information processing in alexithymic

individuals: basic-emotional, cognitive-emotional or mentalizing. It seems that individuals with high alexithymia scores compared to individuals with low scores differ on all three stages of emotional information processing but results are ambiguous. This ambiguity could be due to the inclusion of subjects from different populations and the use of different inclusion criteria in the aforementioned studies. Therefore, we investigate differences in several stages of emotional processing within individuals with high versus low verbalizing scores on the Bermond-Vorst Alexithymia Questionnaire (BVAQ) (Vorst and Bermond, 2001). We test, amongst others, whether individuals with difficulties in verbalizing perform worse on recognition of facial emotional micro-expressions, and on judging the emotional tone of spoken language i.e. prosody. Further, learning to verbalize emotions requires development of an association between particular affective states and particular words and individuals with high levels of alexithymia might be less able to make these associations (Aleman, 2005). Therefore, we include a task in which subjects learn associations between words and emotional facial expressions. Moreover, because deficits in thinking about and interpreting emotions is central to alexithymia, we include an emotional mentalizing task to probe the meta-cognitive level. We expect that participants with high verbalizing scores will show poorer performance on all tasks as compared to participants with low verbalizing scores.

Emotion regulation refers to the conscious or unconscious process used to increase, maintain, or decrease one or more components of an emotional response (Eftekhari et al., 2009). Two emotion regulation strategies have been described and have been widely applied: reappraisal, a cognitive strategy involving reinterpretation of a potentially emotion-eliciting situation into a situation with a different emotional impact, and suppression, a way of response modulation involving inhibition of emotion-expressive behavior. Difficulties in emotion regulation have been proposed to be a core mechanism underlying mood and anxiety disorders. To clarify differences in emotion regulation strategies in relation to alexithymia, we include questionnaires measuring reappraisal and suppression. We expect that participants who score high on verbalizing will use suppression more than reappraisal as emotion regulation strategy.

The *third chapter* focuses on the neural basis of the above mentioned emotion regulation strategies, reappraisal and suppression, in schizophrenia patients, their first-degree relatives and controls. Interestingly, previous studies demonstrated that schizophrenia patients use suppression more than reappraisal as emotion regulation strategy (Livingstone et al., 2009; van der Meer et al., 2009). In this study, we investigate the neural basis underlying reappraisal and suppression in healthy controls, patients with schizophrenia and individuals at increased risk. In addition, we investigate whether these groups show a different use of reappraisal and suppression. We expect that patients as compared to healthy controls and relatives will demonstrate less activation in prefrontal areas during reappraisal of negative stimuli versus attending negative stimuli. To our knowledge, no prior studies investigated emotion processing and the underlying neural mechanisms in relatives. During cognitive processing (working memory task) however, relatives showed compensatory brain activation in the prefrontal cortex (MacDonald et al., 2009). Therefore, relatives might show increased brain activation in the prefrontal cortex during reappraisal. In addition, we expect that controls will benefit most from reappraising negative stimuli (i.e. have lower negative affect rating after reappraising than after just attending negative stimuli), than relatives and that patients will benefit the least from reappraising.

The *fourth chapter* concerns a specific aspect of emotion processing, associative emotional learning, in schizophrenia patients and controls. Associative emotional learning is creating a link between emotional stimuli. Impairments in making an association between a word and an emotional state may lead to difficulties in describing one's feelings with words (emotional verbalizing). Further, the formation of inappropriate associations is regarded to be a possible factor underlying certain symptoms of schizophrenia (Bleuler, 1911). The abnormal functional integration of brain regions has been suggested to be an important pathophysiological mechanism of schizophrenia (dysconnection hypothesis)(Stephan et al., 2009). Most prominently, the prefrontal cortex has been implicated in dysconnectivity in schizophrenia (Friston, 1998). Because associative emotional learning involves multiple underlying processes, recruitment of different task-specific brain regions is essential. Compromised connectivity in brain networks could underlie problems in associative emotional learning and influence emotion processing. Previous studies have already demonstrated that schizophrenia patients show different functional connectivity during both rest and tasks (Calhoun et al., 2009). Therefore, we investigate whether patients with schizophrenia show different functional connectivity during associative emotional learning. In an fMRI scanner, participants are presented with emotional and neutral pictures-word pairs. They have to indicate whether they think the picture and word are associated and to remember the combination. We expect that the network activated during associative emotional learning network will comprise among others amygdala, hippocampus and prefrontal cortex. More specifically, we expect to find decreased functional connectivity in patients between prefrontal cortex and amygdalar-hippocampal complex.

The *fifth chapter* reviews the published evidence on genetically driven variation in neurotransmitter function and brain circuits involved in emotion. We discuss the relationship between genetic polymorphisms, amongst others COMT Val158Met, brain activation and emotion processing. Integration of the emerging evidence suggests that the study of polymorphisms using brain imaging can potentially elucidate biological pathways and mechanisms contributing to individual differences in brain circuits that may bias behavior and affect risk for psychiatric illness.

The *sixth chapter* describes the effect of a genetic polymorphism, COMT Val158Met, on neural activation underlying valence evaluation of emotional words. In addition, the relation between COMT genotype and the ability to describe one's emotions is examined. Valence evaluation requires retrieval of self-related (emotional) information of the word ('what does this word mean to me?'). This process activates regions involved in self-related (emotional) memory. Healthy participants with low and high verbalizing scores have to perform a valence evaluation task in an fMRI scanner and they are tested on alexithymia (BVAQ). Given the evidence suggesting that Met carriers may be less proficient in emotional processing (Weiss et al., 2007a), we expect that Met carriers will report more difficulties in describing their feelings (emotional verbalizing), reflecting susceptibility for emotional disorders. Additionally, we hypothesize that the Met allele carriers will show less activation during valence evaluation in the posterior cingulate cortex as this area has been related to self-related (emotional) processing including autobiographical memory (Maddock, 1999; Maddock et al., 2003), possibly reflecting their lower emotional awareness.

Finally, in *chapter seven* the main findings of this thesis are presented and discussed and directions for future research are given both for scientific purposes and clinical implications.

